

**REMARKS**

First, the undersigned would like to thank the Examiner for the fruitful discussion and helpful suggestions given by the Examiner during the March 30, 2004 telephonic interview about this application. Indeed, per the Examiner's suggestion, enclosed with this response is a Declaration reporting comparative experiments between the claimed invention and the prior art. Also, as recommended by the Examiner, the present response explains in detail the photographs showing the results of the comparative experiment.

This submission is in response to the Official Action dated October 23, 2004. Applicants understand that claims 37 and 38 will be examined upon the allowance of a generic claim. Claims 25-33, 35-38, and 50-55 are pending and at issue. Reconsideration of the above identified application, in view of the following remarks, is respectfully requested.

Claims 25, 53, and 54 have been amended to recite an adherent antimicrobial coating and to recite that the antimicrobial metallic material is bound to the matrix such that the antimicrobial coating does not release biocidal amounts of elutables into the surrounding environment. This is supported throughout the specification, *e.g.*, at page 23, 2<sup>nd</sup> full paragraph, and Example 6, (pp. 37-38).

No new matter has been added by way of this response. Each of the Examiner's rejections are discussed below.

**Sawan Declaration**

Accompanying this amendment is a Declaration under 37 C.F.R. 1.132 by one of the inventors, Dr. Samuel P. Sawan (“Sawan Declaration”), describing differences between the antimicrobial coatings of the claimed invention and the prior art cited in the Office Action.

Also included in the Declaration is a description of a comparative experiment showing that, in contrast to the coated articles of the claimed invention, the coated articles described by the cited prior art release biocidal amounts of elutables into the surrounding environment.

Finally, the prior art catheter tested in the comparative experiment is an ArrowGuard Blue® catheter. In the product description document for the ArrowGuard Blue® catheter, which document accompanies the Sawan Declaration, it is noted that this type of catheter is “a surface treatment that molecularly bonds two agents, chlorhexidine ... and silver sulfadiazine” (page 4, under “Recognized by its blue body...”) and that it is protected by U.S. 5,019,096 to Fox (page 4, Footnote No. 2), which is one of the prior art references cited in the Office Action. Further, the Mermel publication, the second prior art reference cited by the Examiner, discloses that the polyurethane catheter tested a chlorhexidine-silver sulfadiazine-impregnated catheter from Arrow International, the maker of the ArrowGuard Blue® catheter. Accordingly, the prior art catheter to which an article of the invention is compared in the Sawan Declaration is, indeed, a Fox/Mermel-type catheter.

**Examiner Requests**

During the March 30 Interview, the Examiner requested that actual photographs, showing the results of the comparative experiment outlined in the Sawan Declaration, be submitted instead of electronic versions of the same. Accordingly, photographs accompany this response.

The Examiner also requested a detailed explanation of the various features of the photographs. The features shown by the photographs are discussed in the Sawan Declaration, 9<sup>th</sup>

paragraph, and a graphical representation of the photographs, with arrows pointing to relevant areas of the graphical representation and explaining text, accompany this response at Tab 1.

### Anticipation

The Examiner has rejected all claims as allegedly as being anticipated under 35 U.S.C. §102(b) by Mermel et al., 1993 (the “**Mermel Publication**”), contending that the Mermel Publication discloses a catheter coating which exhibits antimicrobial surface activity.

It is respectfully submitted that the Mermel Publication fails to anticipate the claimed invention as set forth by the present claims, for the reasons discussed below and in the Sawan Declaration. To briefly summarize these reasons: in contrast to claims 25, 53, and 54, the polyurethane catheter of the Mermel publication is

- (1) not described as an article comprising an adherent antimicrobial *coating*, but an article *impregnated* with antimicrobial compounds (Mermel, page 920-921, bridging paragraph),
- (2) not an article comprising a *polycationic* polymer matrix, but an article comprising polyurethane, a *nonionic* polymer and chlorhexidine, a low-molecular weight non-polymeric compound (Sawan Declaration, 4<sup>th</sup> paragraph), and
- (3) shown to *release biocidal amounts* into its surrounding environment (Sawan Declaration, 6<sup>th</sup> and 7<sup>th</sup> paragraphs).

Regarding item (2), in polyurethane, the urethane linkage, NH-CO-NH is stable (at least under the conditions employed in the Mermel publication) so that the nitrogens do not become protonated and the carboxyl group does not become anionic. While the Mermel publication also discloses catheters having a heparin coating, heparin is a *polyanionic* polymer. The heparin is bound to urethane by using a benzalkonium chloride (BAK), which is a monocationic biocide. By contrast, the claimed invention calls for the use of a polymeric *polycationic* material. This not taught by the Mermel publication.

Regarding item (3), the articles in the Mermel publication were not only shown to specifically release biocidal amounts into it's environment (Sawan Declaration, 6<sup>th</sup> and 7<sup>th</sup> paragraphs), but presents this quality as desirable. As in the previous amendment, filed September 5, 2003, the Examiner's attention is respectfully directed to the Mermel publication, page 923, 2<sup>nd</sup> column, 3<sup>rd</sup> full paragraph):

It seems increasingly likely that engineering leachable antimicrobial activity onto the surface of a vascular catheter, whether by design or serendipitously in the case of heparin binding, holds much promise for significantly reducing the risk of catheter-related bloodstream infection.

Accordingly, the Mermel publication catheters clearly release, *and are designed to release*, biocidal amounts. This is in direct contrast to the claimed invention.

To show the differences between the present invention and the Mermel Publication in a comparative experiment, a Zone of Inhibition test analyzing the release of biocidal amounts of elutables from an article according to the claimed invention, a Mermel/Fox-type catheter (i.e., a polyurethane-silver sulfadiazine coated catheter), and a control, was performed (see Sawan Declaration, 8<sup>th</sup> and 9<sup>th</sup> paragraphs and Figures 3A-3C). The results of this comparative test clearly show that in contrast to an article according to the invention, a catheter according to the Mermel publication releases biocidal amounts of material from its surface.

For all of these reasons, the Mermel Publication cannot anticipate the claimed invention.

The Examiner has also rejected claims 25-28, 30-32, 35 and 36 as allegedly anticipated under 35 U.S.C. §102(b) by U.S. Patent No. 5,019,096 by Fox et al (the “**Fox Patent**”).

This rejection is respectfully traversed, for the reasons presented in the accompanying Sawan Declaration and for the reasons outlined in the previous response to office action, filed September 5, 2003.

Briefly, the Fox patent describes medical devices having coatings comprising (1) matrix-forming polymers selected from biomedical polyurethane, biomedical silicone, and biodegradable polymers, and (2) antimicrobial agents such as silver salt and chlorhexidine (Fox, Abstract and column 2, lines 9-22). As outlined in the Sawan Declaration (5<sup>th</sup> paragraph) and above, however, the Fox Patent does not teach polycationic polymers, since polyurethane is *non-ionic*, silicone is *polycationic*, and chlorhexidine is a low-molecular weight, *non-polymeric* material. Additionally, a “biodegradable polymer” is, by definition, degraded over time and is therefore *not* an adherent antimicrobial coating, as called for by the claims as amended herewith. Accordingly, the Fox Patent coatings are clearly different from those of the present invention.

Like the Mermel Publication, the Fox Patent catheters are also functionally different from those of the claimed invention, since they release biocidal amounts of elutables, as shown in “zone of inhibition” experiments reported in the Fox Patent (see Sawan Declaration, 6<sup>th</sup> paragraph and page 12, 2<sup>nd</sup> full paragraph of September 5, 2003 response). As with the Mermel Publication, this is by intentional design and a feature described as desirable. As previously noted, the Fox patent’s polyurethane coating is described as follows (Fox Patent, column 4, lines 31-37, emphasis added):

... the essential polymeric coating agent component of the coating vehicle is biomedical polyurethane, since it has been found unexpectedly that polymeric materials of this class enable the antimicrobial agent to be retained in an active state on the coated medical device and released over an appreciable period of time, e.g., from about 12 to in excess of 21 days, ...

Also, claim 1 of the Fox Patent recites, in part:

... wherein the matrix is effective to provide controlled release of the antimicrobial agent at a level sufficient to suppress infection when in contact with fluids ....

The differences between the claimed invention and that of a Mermel/Fox-type catheter are further emphasized by the comparative experiment reported in the Sawan Declaration (see 8<sup>th</sup> and 9<sup>th</sup> paragraphs). The Mermel/Fox-type catheter, in contrast to the exemplary articles of the

invention, released biocidal amounts of elutables into the surrounding environment, sufficient to kill bacteria at a distance from the catheter corresponding to several catheter diameters.

Finally, in the Office Action, the Examiner refers to the following section of the Fox Patent (Fox Patent, column 9):

Some biomedical polyurethanes carry a positive charge and therefore do not react with, and thus inactivate, cationic antimicrobial agents such as Ag or CHA.

However, biomedical polyurethanes that “inactivate” antimicrobial agents would not be effective in the preparation of an antimicrobial coating. Additionally, the Fox Patent provides no examples or descriptions of biomedical polyurethanes which “carry a positive charge” (NB - the claims call for a polycationic polymer) In view of the actual teachings of the Fox Patent, emphasizing the desirability of release of antimicrobial compounds, and the lack of description of even a single polyurethane carrying “a positive charge”, this paragraph cannot be considered to be enabling.

For all of the above reasons, it can be concluded that the Fox Patent antimicrobial coatings differ in both composition and resulting function from the claims as amended herewith. Accordingly, reconsideration and withdrawal of the present rejection is respectfully requested.

#### Double-Patenting

All claims have been rejected by the Examiner under the judicially created doctrine of obviousness-type double-patenting as being allegedly unpatentable over various claims in commonly-owned U.S. Patent 5,849,311.

In response, it is submitted that a terminal disclaimer will be timely filed upon allowance of any conflicting claims in the instant application.

**Conclusion**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: April 23, 2004

Respectfully submitted,

By   
Anna Lövqvist, Ph.D.

Limited Recognition Under  
37 C.F.R. 10.9(b) (see attached)  
Representative of Applicants  
DARBY & DARBY P.C.  
P.O. Box 5257  
New York, New York 10150-5257  
(212) 527-7700  
(212) 753-6237 (Fax)  
Attorneys/Agents For Applicant